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Volume 63
Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals

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Dry Cleaning

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DRY CLEANING
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL: 63 (1995) (p. 33)

4. Summary of Data Reported and Evaluation

4.1 Exposure data

The process of cleaning fabrics with nonaqueous liquids is believed to have begun in France in 1825. The process has evolved into an industry called 'dry cleaning'. 'Camphene' (turpentine) was used initially; in the late 1800s, benzene, benzene soap, naphtha and gasoline began to be used. In the 1920s, Stoddard solvent (mineral spirits or white spirits) was introduced in the United States in order to minimize the fire hazards associated with use of the more volatile hydrocarbon-based solvents. Carbon tetrachloride, the first chlorinated solvent used for dry cleaning, was introduced because of the high cost of petroleum solvents and was widely used until the 1950s. Its use was discontinued because of its toxicity and corrosiveness. Trichloroethylene was introduced in the 1930s. It is still used to a limited extent in Europe and in industrial cleaning plants throughout the world, but it has had a limited market in dry cleaning in the United States because of its incompatibility with acetate dyes.

Use of tetrachloroethylene began to increase in the 1940s, and by the late 1950s it had virtually replaced carbon tetrachloride and trichloroethylene in commercial dry cleaning. Tetrachloroethylene is currently the solvent of choice in most of the world, except in regions, such as Japan, where petroleum-based solvents have remained important in the dry cleaning industry. In 1990, about 53% of the world demand for tetrachloroethylene was for dry cleaning, and about 75% of all dry cleaners used it to clean garments. Chlorofluorocarbon solvents (especially CFC-113) were introduced for use in dry cleaning in the 1970s; however, because of environmental concerns, their use is declining rapidly.

It is estimated that several million people are employed in dry cleaning worldwide. The predominant route of exposure to the solvents used in dry cleaning is by inhalation, although skin absorption and ingestion may also occur. In addition, a wide range of chemicals are used in 'spotting' (treatment of spots); they include chlorinated solvents, amyl acetate, bleaching agents, acetic acid, aqueous ammonia, oxalic acid, hydrogen peroxide and dilute hydrogen fluoride solutions.

Improvements in equipment, solvent reclamation and engineering controls in the dry cleaning industry are resulting in decreasing occupational exposures to chlorinated solvents. The trend to use of 'dry-to-dry' machines, as opposed to the transfer process, has also resulted in reduced emissions and exposures. Typical average exposures to tetrachloroethylene in dry cleaning declined from about 350-700 mg/m3 in the 1970s to 70-350 mg/m3 in the late 1980s. The differences in airborne concentrations between dry cleaning shops are often many times greater than the differences in the exposures of machine operators and other staff within a shop.

4.2 Human carcinogenicity data

The relationship between employment in dry cleaning and the occurrence of cancer has been assessed in proportionate mortality studies, case-control studies and four cohort studies. Two cohort studies restricted to dry-cleaning workers in the United States were given greater weight in the evaluation than were the results of cohort studies of laundry and dry-cleaning workers (from Denmark and Sweden).

The relative risks for mortality from urinary bladder cancer were elevated in both United States cohorts (relative risks of 1.7 and 2.5, total of 17 deaths), with evidence in one of the studies of an increasing risk with

increasing duration of employment. These results are consistent with those from case-control studies in the United States and in Canada and with the findings of a proportionate mortality study in the United States (although the Danish cohort study found no elevated incidence of bladder cancer) and do not appear to be due to confounding by cigarette smoking.

The relative risk for mortality from oesophageal cancer was elevated by a factor of two in both United States cohorts (23 observed deaths in the two studies combined) and increased with increasing duration and/or intensity of employment. This cancer also occurred in slight excess in a proportionate mortality study in the United Kingdom with respect to launderers, dry cleaners and pressers. Risk estimates for oesophageal cancer were not provided in either of the two Nordic studies of laundry and dry cleaning workers. While in a case-control study of oesophageal cancer in Montréal, Canada, none of the case subjects had worked in dry cleaning, the study was relatively small. The relative incidence of oesophageal cancer is increased by consumption of alcohol drinking and cigarette smoking, but potential confounding by these exposures could not be explored directly in these studies.

The relative risk for mortality from cancer of the pancreas was modestly increased in both United States cohort studies; however, this result was not confirmed in two North American case-control studies.

The occurrence of lung cancer was increased slightly in each of the four cohort studies. The mortality rate from lung cancer in the subgroup with long duration of employment and a long interval since first employment (in the one study that evaluated these characteristics) was not elevated. Two case-control studies in North America gave conflicting results.

The relative risk for mortality from cervical cancer was increased by 70-80% in the two United States cohort studies but not at all among Danish dry cleaning and laundry workers. Socioeconomic characteristics were not adjusted for in these studies.

While in a Swedish case-control study and in one of the United States cohort studies moderate increases were found in the relative risk for cancer of the colon in association with employment in dry cleaning, there was no suggestion of an increase in the risk for this form of cancer in the other relevant studies. Furthermore, in the United States cohort study, there was no particular accentuation of the increased risk in relation to increasing duration of employment.

The Danish cohort study of dry cleaning and laundry workers showed some increase in the incidence of cancers of both the liver and the gall-bladder; however, this result was not confirmed in the two United States cohort studies. The results of the case-control studies of liver cancer in the United States are conflicting.

There was a suggestion of an increased risk for non-Hodgkin's lymphoma in one of the two United States cohort studies (relative risk, 1.7, based on seven deaths) and in a large case-control study in the United States; however, no increase in risk for non-Hodgkin's lymphoma was observed in the other United States cohort study, in the Danish cohort study or in a case-control study from Montréal, Canada.

The results of the four cohort studies do not suggest an increase in the risk for cancer of the kidney, while the results of proportionate mortality studies in Wisconsin and Oklahoma and of the case-control studies from Canada, Denmark and the United States indicate an increase in risk associated with a history of work as a dry cleaner. It may be noteworthy that the petroleum solvents used for dry cleaning in Oklahoma are not typical of those used in much of the rest of the world.

Variation within individual studies of dry cleaners may depend on the nature and level of exposure, which varies from shop to shop and across studies of dry cleaning workers. There is also variation in the types of solvents used over time and across geographic regions. These limitations notwithstanding, the epidemiological studies on dry cleaning indicate that the risks for cancers at two sites, urinary bladder and oesophagus, may be increased by employment in dry cleaning.

4.3 Other relevant data

Inconsistent evidence of slight renal damage among workers exposed to tetrachloroethylene in dry cleaning shops was found in two studies, whereas two other studies in which exposure to tetrachloroethylene was at least as high did not find such an association.

Disturbances of sperm quality and fertility have been observed among dry cleaning workers in a few studies of limited size. Several studies performed in Nordic countries have shown a consistent increase in the risk for spontaneous abortion among dry cleaners, but the studies are not entirely independent of each other. No effect has been observed on other reproductive outcomes, such as stillbirth, congenital malformation or low birth weight, but the power of the studies was limited.

In single studies, lymphocytes from dry cleaning workers showed no increase in the frequency of alkaline-labile sites/DNA single-strand breaks. There was inadequate information to evaluate the genetic effects in humans of exposures in dry cleaning.

4.4 Evaluation

There is *limited evidence* in humans for the carcinogenicity of occupational exposures in dry cleaning.

Overall evaluation

Dry cleaning entails exposures that are *possibly carcinogenic to humans (Group 2B).*

For definition of the italicized terms, see Preamble Evaluation.

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TRICHLOROETHYLENE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

Vol.: 63 (1995) (p. 75)
CAS No.: 79-01-6
Chem. Abstr. Name: Trichloroethene

5. Summary and Evaluation

5.1 Exposure data

Trichloroethylene, a chlorinated solvent, has been produced commercially since the 1920s in many countries by chlorination of ethylene or acetylene. Its use in vapour degreasing began in the 1920s. In the 1930s, it was introduced for use in dry cleaning, but it has had limited use in that way since the 1950s. Currently, 80-90% of trichloroethylene worldwide is used for degreasing metals. Use for all applications in western Europe, Japan and the United States in 1990 was about 225 thousand tonnes.

Trichloroethylene has been detected in air, water, soil, food and animal tissues. The most heavily exposed people are those working in the degreasing of metals, who are exposed by inhalation.

5.2 Human carcinogenicity data

Three cohort studies were considered to be particularly relevant for the evaluation of trichloroethylene. Two of these studies, conducted in Sweden and Finland, involved people who had been monitored for exposure to trichloroethylene by measurement of trichloroacetic acid in urine. The levels in samples from most of the people in the two cohorts indicated relatively low levels of exposure. The third study, from the United States, covered workers exposed to trichloroethylene during maintenance of military aircraft and missiles, some of whom were also exposed to other solvents.

A fourth cohort study included all workers in an aircraft manufacturing company in the United States. This study was considered less relevant, as only one-third of the jobs in the plant entailed exposure to trichloroethylene and the exposures of the workers could not be classified.

In none of the available cohort studies was it possible to control for potential confounding factors, such as those associated with social class with regard to cervical cancer and smoking in respect of urinary bladder cancer.

Case-control studies have been conducted to investigate a number of cancer sites, including a multisite study from Montréal, Canada, in which other cancer cases were used as controls. Most of these studies do not provide risk estimates for exposure to trichloroethylene separately but only for groups of chemicals.

The results of the three most informative cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected. The risk for these cancers was not elevated in the fourth, less informative cohort study. Results for liver cancer were given separately in the study from Finland and for the maintenance workers in the study in the United States. A total of seven cases were observed, whereas 4.00 were expected. Three case-control studies of primary liver cancer indicated elevated relative risks for people exposed to solvents, but only a few of the subjects in each study reported exposure to trichloroethylene.

With regard to non-Hodgkin's lymphoma, the results of the three most informative cohort studies were

consistent; the data indicated a modest excess relative risk, with 27 cases observed and 18.9 expected. The risk for non-Hodgkin's lymphoma was not increased in the fourth, less informative study. In a case-control study covering all malignant lymphomas, an elevated odds ratio for exposure to trichloroethylene was indicated on the basis of seven exposed cases. The risk for non-Hodgkin's lymphoma was not increased among people assumed to have been exposed to trichloroethylene in the study in Montréal.

A twofold risk for cervical cancer was observed in two cohort studies.

The occurrence of cancer of the kidney was not elevated in the cohort studies; however, a study of German workers exposed to trichloroethylene revealed five cases of renal cancer whereas no case was found in an unexposed comparison group. The study may, however, have been initiated after the observation of a cluster. A case-control study and the multisite cancer study, both from Montréal, Canada, provided discordant results with regard to cancer of the kidney.

The incidence of urinary bladder cancer was not increased in the two cohort studies from Sweden and Finland, whereas slightly increased numbers of deaths were seen in the two United States cohorts. The incidence of urinary bladder cancer was not increased in people assumed to be exposed to trichloroethylene in the Montréal study.

Data on cancer incidence or mortality have been reported from five areas in which groundwater was contaminated with trichloroethylene. A weak association between contamination and the incidence of leukaemia was indicated in two of these studies, from Massachusetts and New Jersey, United States. The cohort studies of trichloroethylene-exposed workers did not indicate an association with the occurrence of leukaemia. Two studies, from Finland and New Jersey, suggested a marginal increase in the occurrence of non-Hodgkin's lymphoma in areas with contaminated groundwater.

Overall, the most important observations are the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for non-Hodgkin's lymphoma in all three of the most informative cohort studies. Two of these studies reported data for primary liver cancer separately. Finally, the suggested marginally increased risk for non-Hodgkin's lymphoma in areas with trichloroethylene-contaminated groundwater is noted.

5.3 Animal carcinogenicity data

Trichloroethylene, with and without stabilizers, was tested for carcinogenicity by oral administration in two adequate experiments in mice. The studies showed significant increases in the incidences of benign and malignant liver tumours. Of seven studies in which trichloroethylene was given orally to rats, most were inconclusive because of reduced survival or a too short treatment. In two of the studies, the incidence of uncommonly occurring renal-cell tumours was significantly increased in male rats, and in one study an increased incidence of interstitial-cell testicular tumours was seen.

Trichloroethylene was tested for carcinogenicity by inhalation in four experiments in mice. One study showed an increased incidence of lymphomas, one study showed increased incidences of liver tumours, and three studies showed increased incidences of lung tumours. One of three experiments in which rats were exposed by inhalation showed an increased incidence of interstitial testicular tumours and a marginal increase in that of renal-cell tumours in males. No increase in tumour incidence was observed in one study in hamsters exposed by inhalation.

In limited studies, trichloroethylene and its proposed metabolite trichloroethylene oxide did not increase the incidence of skin tumours or local sarcomas in mice when administered by topical application or subcutaneous injection.

5.4 Other relevant data

In rodents, trichloroethylene is rapidly absorbed from the gastrointestinal tract and through the lungs, whereas

absorption of the vapour through the skin is negligible. The major pathway is oxidative metabolism leading to the formation of chloroacetic acids. Mice showed consistently higher rates of oxidative biotransformation than rats. A minor pathway in rodents and humans involves the formation of mercapturic acids.

The acute toxicity of trichloroethylene in rodents and humans is low. After high doses of trichloroethylene are administered repeatedly to rodents, damage is seen in liver and kidney (in mice and rats) and in lung (in mice only). Repeated exposure of humans in the workplace appears to have no marked toxic effects on the kidney or liver. Trichloroethylene is a more potent peroxisome proliferator in the livers of mice than of rats.

The available studies show no consistent effect of trichloroethylene on the human reproductive system. Trichloroethylene is metabolized to trichloroacetic acid in the placenta or fetus of many species. There is little evidence of toxic effects in developing rats or mice.

Studies of structural chromosomal aberrations, aneuploidy and sister chromatid exchange in peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive.

Pure trichloroethylene did not induce chromosomal aberrations, dominant lethal mutations, sister chromatid exchange or unscheduled DNA synthesis in rodents, whereas an increased induction of micronuclei and DNA single-strand breaks/alkaline labile sites was observed.

In single studies with human cells *in vitro*, trichloroethylene of low purity slightly increased the frequencies of sister chromatid exchange and unscheduled DNA synthesis. Pure trichloroethylene did not induce gene mutation in human cells. In mammalian cells *in vitro*, pure trichloroethylene induced cell transformation, sister chromatid exchange and gene mutation, but not chromosomal aberrations. In fungi, trichloroethylene (pure or of unspecified purity) induced aneuploidy, gene mutation and mitotic recombination and induced gene conversion in the presence of metabolic activation.

Gene mutation or DNA damage was usually not induced in prokaryotes by pure trichloroethylene, while preparations containing epoxide stabilizers were mutagenic. Sulfur-containing metabolites formed by a minor trichloroethylene biotransformation pathway were genotoxic in bacteria and cultured renal cells.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of trichloroethylene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of trichloroethylene.

Overall evaluation

Trichloroethylene is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group considered the following evidence:

(i) Although the hypothesis linking the formation of mouse liver tumours with peroxisome proliferation is plausible, trichloroethylene also induced tumours at other sites in mice and rats.

(ii) Several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin's lymphoma.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 364)

Synonyms

- Algylen
- Anamenth
- Chlorilen
- Chlorylen
- Densinfluat
- Ethinyl trichloride
- Ethylene trichloride
- Fluate
- Germalgene
- Narcogen
- Narkosoid
- TCE
- Threthylen
- Threthylene
- Trethylene
- Tri
- Trichloran
- Trichloren
- 1,1,2-Trichlorethylene
- Triclene
- Trielene
- Trielin
- Trieline
- Trilen
- Trilene
- Trimar
- Westrosol

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TETRACHLOROETHYLENE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 159)
CAS No.: 127-18-4
Chem. Abstr. Name: Tetrachloroethene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Tetrachloroethylene is one of the most important chlorinated solvents worldwide and has been produced commercially since the early 1900s. Most of the tetrachloroethylene produced is used for dry cleaning garments; smaller amounts are used in the production of chlorofluorocarbons and for degreasing metals. About 513 thousand tonnes were used in all applications in western Europe, Japan and the United States in 1990.

Tetrachloroethylene has been detected in air, water, food and animal and human tissues. The greatest exposure occurs via inhalation, and workers in dry cleaning and degreasing are the most heavily exposed. Individuals living or working in the vicinity of such operations have been shown to be exposed to lower concentrations.

5.2 Human carcinogenicity data

Results relevant to assessing the relationship between exposure to tetrachloroethylene and cancer risk are available from five cohort studies. In one study in Finland and one in four states of the United States, exposure was specifically to tetrachloroethylene; biological monitoring was conducted in the Finnish study. In a cohort study in Missouri, United States, in which follow-up was from 1948 to 1978, tetrachloroethylene was the chemical to which predominant exposure had occurred since about 1960. Data for a few cancer sites were reported in two other cohort studies, one in Louisiana and one in Utah, United States, in which exposure was to both tetrachloroethylene and other chemicals. Although data on different levels or duration of exposure were available in some of the cohort studies, the number of observed cases in each category was generally too small to allow adequate statistical power for testing for a dose-response relationship. Data from six relevant case-control studies have also been reported.

In the two cohort studies in which results for oesophageal cancer were reported, namely the four-state United States and Missouri studies, the relative risks were 2.6 and 2.1. Lack of data on smoking or alcohol consumption, both strong risk factors for this cancer, indicates caution in interpreting this observation.

The relative risks for cervical cancer were increased in three cohort studies in which such results were reported; however, potential confounding factors associated with socioeconomic status could not be adjusted for.

Elevated relative risks for non-Hodgkin's lymphoma were observed in all three cohort studies in which such results were reported.

With respect to cancer of the kidney, no consistent pattern of elevated risk was seen in the three cohort studies in which such results were reported. Although a case-control study conducted in Montréal, Canada, showed an odds ratio of 3.4, this was not statistically significant, and the exposure in question was to degreasing solvents and not specifically to tetrachloroethylene. In the cohort study in Missouri, the relative risk for urinary bladder cancer was elevated but not statistically significant; little or no information was available

from other studies.

Five studies of people exposed to drinking-water contaminated with tetrachloroethylene have been reported. In four of these, no consistent pattern of risk for any specific cancers was observed. In the fifth study, in Massachusetts, United States, although the increase in the relative risk for leukaemia was significant, the result was based on only two cases. No consistent evidence for an elevated risk for leukaemia was seen in the cohort studies.

In summary, there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma. These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total numbers in the cohort studies combined are relatively small.

5.3 Animal carcinogenicity data

Tetrachloroethylene was tested for carcinogenicity by oral administration in one experiment in mice, and a significant increase in the incidence of hepatocellular carcinomas was observed in animals of each sex. A study in rats treated orally was inadequate for an evaluation of carcinogenicity. Tetrachloroethylene was tested for carcinogenicity by inhalation in one experiment in mice and in one experiment in rats. The incidence of hepatocellular adenomas and carcinomas was significantly increased in mice of each sex, and the incidence of mononuclear-cell leukaemia was significantly increased in rats of each sex. A nonsignificant increase in the incidence of uncommonly occurring renal-cell adenomas and adenocarcinomas was also observed in male rats. Tetrachloroethylene did not induce skin tumours in mice after administration by topical application in one study.

A presumed metabolite of tetrachloroethylene, tetrachloroethylene oxide, did not increase the incidence of local tumours in mice when given by topical application or subcutaneous injection.

5.4 Other relevant data

Tetrachloroethylene is rapidly absorbed after inhalation and from the gastrointestinal tract, but dermal absorption from the gaseous phase is negligible. The biotransformation of tetrachloroethylene is species- and dose-dependent; mice consistently had a greater capacity to biotransform tetrachloroethylene than rats. Two metabolic pathways have been demonstrated in rodents: cytochrome P450-catalysed oxidation and, as a minor route, glutathione conjugation.

Tetrachloroethylene shows only low acute toxicity in humans and in experimental animals. After repeated administration, the major target organ is the liver in mice and the kidney in rats. Tetrachloroethylene induced peroxisome proliferation in mouse liver after oral administration; a marginal response was observed in mouse kidney and rat liver.

Disturbances of sperm quality and fertility have been observed among dry cleaners exposed to tetrachloroethylene in a few studies of limited size. The results of studies of women exposed to tetrachloroethylene in dry cleaning shops and other settings are generally consistent in showing an increase in the rate of spontaneous abortions; however, other solvents were also present in most of these workplaces. Effects on other reproductive outcomes such as stillbirths, congenital malformations and low birth weight could not be evaluated in these studies.

Tetrachloroethylene can cross the placenta of rats and is metabolized in the placenta or fetus to trichloroacetic acid. Tetrachloroethylene appears to have little toxicity in developing rats and rabbits; high atmospheric concentrations produced delayed fetal development in mice in one study.

The frequencies of gene conversion and gene mutation were not increased in yeast recovered from mice treated with tetrachloroethylene *in vivo*. Tetrachloroethylene increased the frequency of DNA single-strand

breakage/alkaline-labile sites in the liver and kidney of mice *in vivo* in one study, but binding to DNA was not demonstrated in mouse liver.

It did not induce gene mutation (in a single study), chromosomal aberrations, sister chromatid exchange (in a single study) or DNA damage in mammalian cells *in vitro.* In single studies, it induced morphological transformation in virus-infected rat embryo cells but not in BALBc/3T3 cells. The only study available showed no induction of gene mutation by tetrachloroethylene in insects. Tetrachloroethylene did not usually induce gene conversion in yeasts; the results with regard to induction of aneuploidy in one study were inconclusive. Tetrachloroethylene did not increase the frequency of mutations in bacteria, except in one study in which a metabolic activation system consisting of liver and kidney fractions, which favours glutathione conjugation and further activation, was used. The metabolites formed from tetrachloroethylene in rats by minor biotransformation pathways, *S*-1,2,2-trichloroglutathione and derived sulfur conjugates, were genotoxic in bacteria and cultured renal cells.

The frequency of H-*ras* mutations was lower in hepatocellular tumours from tetrachloroethylene-treated mice than in tumours from control animals, whereas the frequency in hepatocellular tumours from trichloroethylene-treated mice was not significantly different from that in controls. The frequency of K-*ras* mutations was higher in liver tumours from tetrachloroethylene-treated mice than in tumours from control animals.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of tetrachloroethylene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetrachloroethylene.

Overall evaluation

Tetrachloroethylene is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group considered the following evidence:

(i) Although tetrachloroethylene is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferation and tumour formation in the liver after administration of tetrachloroethylene by inhalation. The spectrum of mutations in proto-oncogenes in liver tumours from mice treated with tetrachloroethylene is different from that in liver tumours from mice treated with trichloroethylene.

(ii) The compound induced leukaemia in rats.

(iii) Several epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma and cervical cancer.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 355)

Synonyms

- Ethylene tetrachloride
- PCE
- 'per'
- PER
- Perchlorethylene

- Perchloroethene
- Perchloroethylene
- Tetrachlorethylene
- 1,1,2,2-Tetrachloroethene
- 1,1,2,2-Tetrachloroethylene

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1,2,3-TRICHLOROPROPANE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 223)
CAS No.: 96-18-4
Chem. Abstr. Name: 1,2,3-Trichloropropane

5. Summary and Evaluation

5.1 Exposure data

1,2,3-Trichloropropane, a chlorinated solvent, has been produced commercially for use as a paint and varnish remover and as a cleaning and degreasing agent. Currently, it is used primarily as a chemical intermediate. It has been detected in water, including drinking-water, and in soil as a result of its presence as an impurity in a commercial nematocide.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1,2,3-Trichloropropane was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. It produced tumours of the oral mucosa and of the uterus in female mice and increased the incidences of tumours of the forestomach, liver and Harderian gland in mice of each sex. In rats, increased incidences of tumours were observed in the preputial gland, kidney and pancreas of males, in the clitoral gland and mammary gland of females and in the oral cavity and forestomach of both males and females.

The metabolite, 1,3-dichloroacetone, initiated skin tumour development in mice when applied topically.

5.4 Other relevant data

No data are available on the toxicokinetics of 1,2,3-trichloropropane in humans. It is rapidly absorbed and excreted after oral administration to rats and mice. Its metabolic products bind covalently to rat hepatic protein and DNA. The reactive and mutagenic metabolite, 1,3-dichloroacetone, was formed by hepatic metabolism in rat and human microsomes *in vitro*.

1,2,3-Trichloropropane causes tissue necrosis in a number of organs in rats and mice; the liver and kidney are the main target organs in the rat. In addition, myocardial and nasal epithelial damage is observed; in mice, hepatic and bronchiolar necrosis are seen.

There are no data on the effects of 1,2,3-trichloropropane on human reproduction. Studies performed in rats provided no evidence of alteration of fertility or of embryotoxic effects. In a two-generation study in mice, there was evidence of impairment of the female reproductive system.

In single studies, DNA binding and induction of DNA breaks, but not of dominant lethal mutations, were reported in rodents treated *in vivo*.

Gene mutation, sister chromatid exchange and chromosomal aberrations, but not DNA damage, were induced

in rodent cells *in vitro* (all single studies, except for sister chromatid exchange). 1,2,3-Trichloropropane was mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,2,3-trichloropropane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2,3-trichloropropane.

Overall evaluation

1,2,3-Trichloropropane *is probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into account the following evidence:

(i) 1,2,3-Trichloropropane causes tumours at multiple sites and at high incidence in mice and rats.

(ii) The metabolism of 1,2,3-trichloropropane is qualitatively similar in human and rodent microsomes.

(iii) 1,2,3-Trichloropropane is mutagenic to bacteria and to cultured mammalian cells and binds to DNA of animals treated *in vivo***.**

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Allyl trichloride
- Glycerol trichlorohydrin
- Glyceryl trichlorohydrin
- Trichlorohydrin
- Trichloropropane

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CHLORAL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 245)
CAS No.: 75-87-6
Chem. Abstr. Name: Trichloroacetaldehyde

CHLORAL HYDRATE
(Group 3)

VOL.: 63 (1995) (p. 245)
CAS No.: 302-17-0
Chem. Abstr. Name: 2,2,2-Trichloro-1,1-ethanediol

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Chloral has been produced commercially since the 1940s by chlorination of ethanol. Until the early 1970s, its major use was in the production of the insecticide DDT. Chloral is also used as an intermediate in the production of the insecticides methoxychlor, naled, trichlorfon and dichlorvos, the herbicide trichloroacetic acid and the hypnotic drugs chloral hydrate, chloral betaine, -chloralose and triclofos sodium.

Human exposure to chloral (or its hydrate) can occur during its production and use, from drinking chlorinated water and from pharmaceutical use.

Chloral is rapidly converted to its hydrate in contact with aqueous solutions.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Chloral hydrate was tested for carcinogenicity in one adequate study in male mice by oral administration. It increased the incidence of hepatocellular adenomas and carcinomas.

5.4 Other relevant data

Chloral hydrate is metabolized rapidly in both humans and experimental animals to trichloroethanol and trichloroacetate. Its main acute toxic effects in humans are inhibition of respiration and induction of cardiac arrhythmia. Repeated administration of chloral hydrate damages the liver in mice and in male rats. Exposure of mice by inhalation results in damage to Clara cells in the lung.

Chloral hydrate crosses the human placenta, but there have been no reports of adverse results other than an increased likelihood of hyperbilirubinaemia in infants. No malformations and no effect on development were observed in the offspring of mice administered chloral throughout gestation.

Chloral hydrate is a well-established aneuploidogenic agent. It clearly induced aneuploidy and micronuclei in mammals treated *in vivo*, whereas chromosomal aberrations were not found in most studies. Conflicting results were obtained with regard to the induction of DNA damage in mammals treated with chloral hydrate *in vivo*.

Chloral hydrate induced aneuploidy and micronuclei in cultured human cells *in vitro*, but the results with regard to the induction of sister chromatid exchange were inconclusive. In rodent cells *in vitro*, chloral hydrate increased the induction of micronuclei but did not induce DNA damage; chromosomal aberrations were induced in a single study *in vitro*. In fungi, chloral hydrate clearly induced aneuploidy, while the results of studies on mitotic recombination and gene conversion were inconclusive. A single study showed induction of somatic mutation by chloral hydrate in insects. The results of assays for mutagenicity in bacteria were inconsistent.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of chloral and chloral hydrate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of chloral.

There is *limited evidence* in experimental animals for the carcinogenicity of chloral hydrate.

Overall evaluation

Chloral and chloral hydrate are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Subsequent evaluation: Vol. 85 (2004)

Synonyms for chloral

- Anhydrous chloral
- Grasex
- Sporotal 100
- 2,2,2-Trichloroacetaldehyde
- Trichloroethanal
- 2,2,2-Trichloroethanal

Synonyms for chloral hydrate

- Aquachloral
- Bi 3411
- Chloral monohydrate
- Dormal
- EPA Pesticide Chemical Code 268100
- Felsules
- Hydral
- Kessodrate
- Lorinal
- Noctec
- Nycoton
- Nycton
- Phaldrone

- Rectules
- Somnos
- Sontec
- Tosyl
- Trawotox
- Trichloroacetaldehyde hydrate
- Trichloroacetaldehyde monohydrate
- 1,1,1-Trichloro-2,2-dihydroxyethane

Last Updated 05/22/97

DICHLOROACETIC ACID
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 271)
CAS No.: 79-43-6
Chem. Abstr. Name: Dichloroacetic acid

5. Summary and Evaluation

5.1 Exposure data

Dichloroacetic acid is produced commercially in small quantities for use as an intermediate in the production of glyoxylic acid, dialkyloxy and diaryloxy acids and sulfonamides. Human exposure may occur during the production and use of dichloroacetic acid and from drinking chlorinated water.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of dichloroacetic acid to humans.

5.3 Animal carcinogenicity data

Neutralized dichloroacetic acid was tested by oral administration in males of one strain of mice in four studies. Increased incidences of hepatocellular adenomas and carcinomas were observed in all of the studies.

5.4 Other relevant data

Dichloroacetic acid is metabolized in humans and experimental animals, and oxalate, thiodiacetic acid and unchanged dichloroacetic acid are excreted in urine. Clearance is decreased in humans after repeated administration. Species differences in the clearance of dichloroacetic acid are observed in rodents: clearance in rats is much slower than in mice. Dichloroacetic acid induces peroxisome proliferation in the livers of both rats and mice.

No data were available on the effects of dichloroacetic acid on human reproduction. In rats and dogs, testicular degeneration can occur after exposure to this compound. The development of the heart, major vessels and kidney of rats can be affected by exposure *in utero*.

The evidence for induction of DNA strand breaks in liver cells of rodents exposed to dichloroacetic acid *in vivo* was inconclusive. Strand breaks were not induced in human or rodent cells *in vitro*. The results of assays for mutagenesis in bacteria were inconsistent.

The spectrum of mutations in H-*ras* proto-oncogenes in hepatic tumours from mice treated with dichloroacetic acid was different from that seen in hepatic tumours from untreated mice.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of dichloroacetic acid.

There is *limited evidence* in experimental animals for the carcinogenicity of dichloroacetic acid.

Overall evaluation

Dichloroacetic acid *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Subsequent evaluation: Vol. 84 (2004)

Synonyms

- Bichloracetic acid
- DCA
- DCA (acid)
- DCAA
- Dichloracetic acid
- Dichlorethanoic acid
- Dichloroethanoic acid
- 2,2-Dichloroethanoic acid

Last updated 05/27/1997

TRICHLOROACETIC ACID
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 291)
CAS No.: 76-03-9
Chem. Abstr. Name: Trichloroacetic acid

5. Summary and Evaluation

5.1 Exposure data

Trichloroacetic acid is produced commercially in small amounts by chlorination of acetic or chloroacetic acid. It is used principally in the form of the sodium salt, as a herbicide. Most human exposure to trichloroacetic acid occurs because of its metabolic formation from tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane and chloral hydrate. Trichloroacetic acid can also be formed during the chlorination of drinking-water.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of trichloroacetic acid to humans.

5.3 Animal carcinogenicity data

Trichloroacetic acid was tested by oral administration in the drinking-water in two studies in males of one strain of mice. In both studies, the incidence of hepatocellular adenomas and carcinomas was increased.

5.4 Other relevant data

Trichloroacetic acid has a longer plasma half-life in humans than in rodents, presumably because there is more binding to plasma proteins in humans. Much of an administered dose of trichloroacetic acid is excreted unchanged in the urine of rats and mice. Reductive dechlorination and glutathione conjugation are involved in the formation of the urinary metabolites, oxalate and thiodiacetic acid.

Little is known about the toxicity of this compound to humans. Single doses of high concentrations of trichloroacetic acid induce lipid peroxidation in the livers of rats and mice. Trichloroacetic acid causes hepatic peroxisome proliferation in both rats and mice *in vivo* and in cultured hepatocytes from mice and rats, but not from humans. Short-term, repeated administrations of trichloroacetic acid induced cell proliferation in the livers of mice but reduced cell proliferation in the livers of rats.

No data were available on the effects of trichloroacetic acid on human reproduction. In rats, fetotoxicity was observed at doses that are maternally toxic.

Trichloroacetic acid induced chromosomal aberrations and abnormal sperm in mice in one study. The results of studies on the induction of DNA strand breaks and micronuclei were inconclusive.

Trichloroacetic acid did not induce chromosomal aberrations in a single study or DNA strand breaks in cultured mammalian cells. Inhibition of intercellular communication has been reported. It was not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of trichloroacetic acid.

There is *limited evidence* in experimental animals for the carcinogenicity of trichloroacetic acid.

Overall evaluation

Trichloroacetic acid *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Subsequent evaluation: Volume 84 (2004)

Synonyms

- Aceto-Caustin
- Amchem Grass Killer
- TCA
- TCAA
- TCA (acid)
- Trichloracetic acid
- Trichloroethanoic acid
- Trichloromethanecarboxylic acid

Last updated 05/27/1997

1-CHLORO-2-METHYLPROPENE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 315)
CAS No.: 513-37-1
Chem. Abstr. Name: 1-Chloro-2-methyl-1-propene

5. Summary and Evaluation

5.1 Exposure data

1-Chloro-2-methylpropene occurs as an impurity in the production of 3-chloro-2-methylpropene. It has no known commercial application.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

1-Chloro-2-methylpropene was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. It produced squamous-cell carcinomas of the preputial gland in male mice and squamous-cell carcinomas of the forestomach in animals of each sex. In rats, it produced carcinomas of the nasal cavity and papillomas and carcinomas of the oral cavity, oesophagus and forestomach in animals of each sex.

5.4 Other relevant data

No data were available on the toxicokinetics or toxic effects of 1-chloro-2-methylpropene in humans. It is rapidly absorbed and excreted after oral administration to rats and mice. In rats, more of the dose was excreted via the lungs than in the urine, whereas in mice similar proportions were excreted by the two routes. Both the unchanged compound and carbon dioxide were exhaled. The major urinary metabolite in rats and mice was formed after oxidation and glutathione conjugation.

Repeated oral administration of 1-chloro-2-methylpropene to rats resulted in tissue necrosis in a number of organs, including the small and large intestine, thymus and spleen. Repeated administration of the compound to rats by gavage induced proliferation of forestomach cells.

Gene mutation and sister chromatid exchange, but not chromosomal aberrations, were induced in cultured rodent cells in single studies. 1-Chloro-2-methylpropene induced gene and chromosomal mutation in insects (in a single study). It was mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1-chloro-2-methylpropene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-chloro-2-methylpropene.

Overall evaluation

1-Chloro-2-methylpropene *is possibly carcinogenic to humans (Group 2B)*. For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- α-Chloroisobutylene
- 1-Chloroisobutylene
- Dimethylvinyl chloride
- 2,2-Dimethylvinyl chloride
- β,β-Dimethylvinyl chloride
- Isocrotyl chloride
- 2-Methyl-1-chloropropene
- 2-Methyl-1-propenyl chloride

Last updated 05/27/1997

3-CHLORO-2-METHYLPROPENE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 325)
CAS No.: 563-47-3
Chem. Abstr. Name: 3-Chloro-2-methyl-1-propene

5. Summary and Evaluation

5.1 Exposure data

3-Chloro-2-methylpropene is produced commercially as a chemical intermediate. It has had limited use as an insecticide and grain fumigant.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

3-Chloro-2-methylpropene containing 5% 1-chloro-2-methylpropene (see monograph, p. 315) was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. Tumours of the forestomach were induced in mice and rats of each sex.

5.4 Other relevant data

No data were available on the toxicokinetics or toxic effects of 3-chloro-2-methylpropene in humans. It is rapidly absorbed, extensively metabolized and rapidly excreted after oral administration to rats. Most of the excretory products were found in urine; a mercapturic acid was the main metabolite. Considerable amounts were exhaled, some as carbon dioxide.

After repeated oral administrations, 3-chloro-2-methylpropene induced liver necrosis in rats and mice and kidney necrosis in mice; it also induced forestomach hyperplasia in rats.

No data were available on the effects of 3-chloro-2-methylpropene on reproduction in humans or experimental animals.

Micronuclei were not induced in the bone marrow of mice treated *in vivo* in a single study. 3-Chloro-2-methylpropene induced gene mutation, sister chromatid exchange and chromosomal aberrations in rodent cells in single studies. It was mutagenic to insects and bacteria. The genotoxic effects of this compound cannot be attributed solely to the presence of 1-chloro-2-methylpropene as an impurity.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 3-chloro-2-methylpropene.

There is *limited evidence* in experimental animals for the carcinogenicity of 3-chloro-2-methylpropene.

Overall evaluation

3-Chloro-2-methylpropene *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- 3-Chloroisobutene
- γ-Chloroisobutylene
- 3-Chloroisobutylene
- 2-(Chloromethyl)-1-propene
- Isobutenyl chloride
- MAC
- Methallylchloride
- β-Methylallylchloride
- Methallyl chloride
- β-Methallyl chloride
- 2-Methallyl chloride
- Methylallyl chloride
- 2-Methylallyl chloride
- 2-Methyl-3-chloropropene
- 2-Methyl-2-propenyl chloride

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ACROLEIN
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 337)
CAS No.: 107-02-8
Chem. Abstr. Name: 2-Propenal

5. Summary and Evaluation

5.1 Exposure data

Acrolein has been produced commercially since the 1940s. It is used mainly in the production of acrylic acid, a starting material for acrylate polymers. It is also used in the production of DL-methionine and as a herbicide and slimicide.

Acrolein occurs naturally in foods and is formed during the combustion of fossil fuels (including engine exhausts), wood and tobacco and during the heating of cooking oils. Human exposure occurs from these sources and during its production and use.

5.2 Human carcinogenicity data

The available data were inadequate to form the basis for an evaluation of the carcinogenicity of acrolein to humans.

5.3 Animal carcinogenicity data

Acrolein was tested for carcinogenicity in one experiment in mice and in two experiments in rats by oral administration. No increase in tumour incidence was observed in mice or in rats in the one adequate study.

An increased incidence of urinary bladder papillomas was observed in rats receiving intraperitoneal injections of acrolein in combination with uracil in the diet.

5.4 Other relevant data

Acrolein is retained irreversibly in the respiratory tract after exposure by inhalation, probably because of its high tissue reactivity. Consequently, there is little, if any, distribution to other organs. Subcutaneous and oral exposure and long-term inhalation result in some systemic distribution and urinary excretion. Acrolein reacts readily with reduced glutathione, and this is the dominant detoxification pathway.

Acrolein is an intense irritant, and its irritancy may limit exposure to this substance. Repeated inhalation results in changes in the upper and lower respiratory tract. In dogs, acute congestion, changes in bronchiolar epithelial cells and emphysema were found after inhalation of the lowest dose tested.

No data were available on the effects of acrolein on human reproduction. No reproductive toxicity was seen in rats or rabbits treated with acrolein by gavage.

In single studies, acrolein did not induce DNA damage in rats or dominant lethal mutations in mice treated *in vivo*.

In cultured mammalian cells, acrolein induced gene mutation, sister chromatid exchange and DNA damage; weak induction of chromosomal aberrations was observed in one study.

Acrolein induced both somatic and germinal mutations in insects and DNA mutation and DNA damage in bacteria. DNA binding *in vitro* was observed in several studies.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of acrolein.

There is *inadequate evidence* in experimental animals for the carcinogenicity of acrolein.

Overall evaluation

Acrolein *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 78)

Synonyms

- Acraldehyde
- Acrylaldehyde
- Acrylic aldehyde
- Allyl aldehyde
- Aqualin
- Ethylene aldehyde
- Magnacide B
- Magnacide H
- Propenal
- Prop-2-en-1-al

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CROTONALDEHYDE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 373)

CAS No.: 4170-30-3
Chem. Abstr. Name: 2-Butenal

CAS No.: 15798-64-8
Chem. Abstr. Name: (*Z*)-2-Butenal (*cis*-isomer)

CAS No.: 123-73-9
Chem. Abstr. Name: (*E*)-2-Butenal (*trans*-isomer)

5. Summary and Evaluation

5.1 Exposure data

Crotonaldehyde is produced principally as an intermediate for the production of sorbic acid. It was formerly used in large amounts in the production of *n*-butanol.

Crotonaldehyde occurs naturally in foods and is formed during the combustion of fossil fuels (including engine exhausts), wood and tobacco and in heated cooking oils. Human exposure occurs from these sources and may occur during its production and use.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of crotonaldehyde to humans.

5.3 Animal carcinogenicity data

Crotonaldehyde was tested for carcinogenicity in one study in male rats by administration in the drinking-water. Increased incidences of hepatic neoplastic nodules and altered liver-cell foci were seen, but these were not dose-related.

5.4 Other relevant data

Crotonaldehyde is a substrate for aldehyde dehydrogenase and forms conjugates with glutathione, in the presence or absence of glutathione transferase. Mercapturic acid metabolites have been identified in urine.

Crotonaldehyde is a potent irritant, and it has been reported to interfere with immune function.

Crotonaldehyde did not induce DNA damage in rat hepatocytes *in vitro* in a single study. It was mutagenic to insects and bacteria. It bound to DNA of mouse skin *in vivo* after topical application and to DNA *in vitro* and caused formation of DNA-protein cross-links.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of crotonaldehyde.

There is *inadequate evidence* in experimental animals for the carcinogenicity of crotonaldehyde.

Overall evaluation

Crotonaldehyde *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms for Crotonaldehyde

- 2-Butenaldehyde
- Crotonal
- Crotonic aldehyde
- Crotylaldehyde
- 1-Formylpropene
- β-Methylacrolein
- Propylene aldehyde

Synonyms for *cis* Isomer

- *cis*-2-Butenal
- *cis*-Crotonaldehyde

Synonyms for *trans* Isomer

- 2(*E*)-Butenal
- *trans*-2-Butenal
- *trans*2-Buten-1-al
- *trans*-Crotonal
- *trans*-Crotonaldehyde
- Topanel CA

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FURAN
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 393)
CAS No.: 110-00-9
Chem. Abstr. Name: Furan

5. Summary and Evaluation

5.1 Exposure data

Furan is produced commercially by decarbonylation of furfural. It is used mainly in the production of tetrahydrofuran, thiophene and pyrrole. It also occurs naturally in certain woods and during the combustion of coal and is found in engine exhausts, wood smoke and tobacco smoke.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Furan was tested for carcinogenicity by oral administration in one study in mice and in one study in rats. It produced hepatocellular adenomas and carcinomas in mice. In rats, it produced hepatocellular adenomas in animals of each sex and carcinomas in males; a high incidence of cholangiocarcinomas was seen in both males and females. The incidence of mononuclear-cell leukaemia was also increased in animals of each sex.

5.4 Other relevant data

Furan is rapidly and extensively absorbed by rats after oral administration; part of the absorbed dose becomes covalently bound to protein, mainly in the liver. No DNA binding could be demonstrated in the liver.

Repeated administration of furan to mice and rats leads to liver necrosis, liver-cell proliferation and bile-duct hyperplasia; in rats, prominent cholangiofibrosis develops.

Induction of chromosomal aberrations but not of sister chromatid exchange was observed in rodents treated *in vivo* in one study. Gene mutation, sister chromatid exchange (in single studies) and chromosomal aberrations were induced in rodent cells *in vitro*.

Furan was not mutagenic to insects or bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of furan.

There is *sufficient evidence* in experimental animals for the carcinogenicity of furan.

Overall evaluation

Furan is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Axole
- Divinylene oxide
- 1,4-Epoxy-1,3-butadiene
- Furfuran
- Furfurane
- Oxacyclopentadiene
- Oxole
- Tetrol
- Tetrole
- U124

Last updated 05/27/1997

FURFURAL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 409)
CAS No.: 98-01-1
Chem. Abstr. Name: 2-Furancarboxaldehyde

5. Summary and Evaluation

5.1 Exposure data

Furfural is produced commercially by the acid hydrolysis of pentosan polysaccharides from non-food residues of food crops and wood wastes. It is used widely as a solvent in petroleum refining, in the production of phenolic resins and in a variety of other applications. Human exposure to furfural occurs during its production and use, as a result of its natural occurrence in many foods and from the combustion of coal and wood.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Furfural was tested for carcinogenicity by oral administration in one study in mice and one study in rats. In mice, it increased the incidence of hepatocellular adenomas and carcinomas in males and of hepatocellular adenomas and forestomach papillomas in females. Male rats had a low incidence of cholangiocarcinomas, which occur rarely. In a two-stage assay on mouse skin, furfural had weak initiating activity.

5.4 Other relevant data

Furfural is extensively absorbed and rapidly eliminated after inhalation by humans and rats. Furfural in air is also absorbed dermally by humans. Repeated exposure of hamsters to furfural by inhalation severely damages the olfactory epithelium. Repeated oral administration to rats causes liver necrosis and cirrhosis.

Neither chromosomal aberrations nor sister chromatid exchanges were observed in rodents treated with furfural *in vivo* in a single study.

Gene mutation (in a single study), sister chromatid exchange and chromosomal aberrations were induced in mammalian cells *in vitro*. Sex-linked recessive lethal mutations were induced in insects. Furfural induced weak or no mutagenicity in bacteria but damaged DNA *in vitro*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of furfural.

There is *limited evidence* in experimental animals for the carcinogenicity of furfural.

Overall evaluation

Furfural *is not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Artificial ant oil
- 2-Formylfuran
- Fural
- Furaldehyde
- 2-Furanaldehyde
- 2-Furancarbaldehyde
- Furancarbonal
- 2-Furancarbonal
- 2-Furfural
- Furfuraldehyde
- 2-Furfuraldehyde
- Furfurol
- Furfurole
- Furfurylaldehyde
- Furole
- α-Furole
- 2-Furylaldehyde
- 2-Furylcarboxaldehyde
- Pyromucic aldehyde

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BENZOFURAN
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 431)
CAS No.: 271-89-6
Chem. Abstr. Name: Benzofuran

5. Summary and Evaluation

5.1 Exposure data

Benzofuran is produced by isolation from coal-tar oils, which are obtained as by-products of coking coal. Its major use is in the production of coumarone-indene resins. Human exposure can occur during coke production, coal gasification, the production of coumarone-indene resins or the combustion of coal and from tobacco smoke.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Benzofuran was tested for carcinogenicity by oral administration in one study in mice and in one study in rats. In mice, benzofuran increased the incidence of hepatocellular adenomas in animals of each sex and of hepatoblastomas and forestomach papillomas and carcinomas in males; the incidence of alveolar-bronchiolar adenomas was increased in both males and females. Female rats had an increased incidence of renal-cell adenocarcinomas, which occur rarely in animals of this sex.

5.4 Other relevant data

No data were available on the toxicokinetics of benzofuran. Repeated administration of benzofuran to rats and mice caused renal toxicity; rats also developed slight hepatic toxicity.

Induction of gene mutation, sister chromatid exchange and chromosomal aberrations was seen in cultured rodent cells treated with benzofuran in single studies. Benzofuran was not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of benzofuran.

There is *sufficient evidence* in experimental animals for the carcinogenicity of benzofuran.

Overall evaluation

Benzofuran is possibly carcinogenic to humans (Group 2B).

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- AT 33852
- Benzo[*b*]furan
- 2,3-Benzofuran
- Benzofurfuran
- 2,3-Benzofurfuran
- Coumarone
- Cumarone
- 1-Oxindene
- R 7204

Last updated 05/27/1997

VINYL ACETATE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 443)
CAS No.: 108-05-4
Chem. Abstr. Name: Acetic acid, ethenyl ester

5. Summary and Evaluation

5.1 Exposure data

Vinyl acetate is used in the production of a wide range of polymers, including polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate copolymers and polyvinyl chloride-vinyl acetate copolymers, which are widely used in the production of adhesives, paints and food packaging.

Human exposure to vinyl acetate occurs mainly by inhalation or dermal contact during production of the monomer or during production of polymers and water-based paints.

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of vinyl acetate to humans.

5.3 Animal carcinogenicity data

Vinyl acetate was tested in one experiment in mice and in one experiment in rats by inhalation. No treatment-related increase in tumour incidence was observed in mice; in rats, an increased incidence of nasal cavity tumours was found in animals of each sex. No increase in tumour incidence was found in rats administered vinyl acetate in the drinking-water *in utero* and then for life.

5.4 Other relevant data

Vinyl acetate is rapidly metabolized by esterases in human blood and animal tissues to acetaldehyde and acetic acid.

Vinyl acetate irritates the eye and respiratory system. Respiratory distress is seen after subchronic exposure by inhalation. Other effects included nasal irritation, nasal mucosal metaplasia, tracheal metaplasia and bronchitis or bronchiolitis. After chronic exposure by inhalation, changes were observed in the lung. Non-neoplastic effects, atrophic and regenerative changes, were seen in the nasal cavity. After chronic exposure via the drinking-water, the only effects observed were decrements in body weight at high doses.

There are no data on the effects of vinyl acetate on human reproduction. A two-generation study in rats showed evidence of parental toxicity and decreased fertility at the highest dose tested. Oral administration of vinyl acetate to rats during pregnancy did not result in maternal or developmental toxicity, whereas exposure by inhalation induced maternal toxicity, retarded embryonic growth and minor skeletal alterations at the highest dose tested.

Vinyl acetate induced sperm abnormalities and sister chromatid exchange in rodents exposed *in vivo*; micronuclei were induced in bone marrow but not in meiotic cells. No DNA binding was seen in rat

hepatocytes. In human lymphocytes *in vitro*, vinyl acetate produced chromosomal aberrations, micronuclei, sister chromatid exchange and DNA cross-links. It enhanced viral transformation and sister chromatid exchange in mammalian cells *in vitro*, and it induced DNA-protein cross-links in rat nasal epithelial cells *in vitro*. Vinyl acetate did not induce mutation in bacteria but induced DNA-protein cross-links in plasmid DNA. The primary metabolite of vinyl acetate, acetaldehyde, is genotoxic in a wide range of assays.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vinyl acetate.

There is *limited evidence* in experimental animals for the carcinogenicity of vinyl acetate.

Overall evaluation

Vinyl acetate *is possibly carcinogenic to humans (Group 2B)*.

In making the overall evaluation, the Working Group took into account the following evidence:

(i) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.

(ii) There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1987). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.

(iii) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 73)

Synonyms

- Acetoxyethene
- Acetoxyethylene
- 1-Acetoxyethylene
- Ethenyl acetate
- Ethenyl ethanoate
- VA
- VAC
- VAM
- Vinyl A monomer
- Vyac
- Zeset T
- RP 251

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VINYL FLUORIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 63 (1995) (p. 467)
CAS No.: 75-02-5
Chem. Abstr. Name: Fluoroethene

5. Summary and Evaluation

5.1 Exposure data

Vinyl fluoride has been produced commercially since the 1960s for use in the production of polyvinylfluoride and fluoropolymers. Human exposure may occur during its production and use.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vinyl fluoride was tested for carcinogenicity in one experiment in mice and one experiment in rats by inhalation. It produced haemangiosarcomas in the liver and alveolar-bronchiolar adenomas in mice of each sex, mammary tumours in females and Harderian gland adenomas in males. In rats, it produced haemangiosarcomas of the liver and Zymbal gland tumours in animals of each sex and an increased incidence of hepatocellular adenomas and carcinomas in females.

5.4 Other relevant data

Vinyl fluoride is readily absorbed after administration by inhalation. Its metabolism is saturable and dose-dependent. Vinyl fluoride has very low acute toxicity. High doses produced no measurable toxic effects after subchronic exposure. Survival was decreased after chronic exposure, but no other toxic effects were seen in surviving animals.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vinyl fluoride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl fluoride.

Overall evaluation

Vinyl fluoride *is probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into account the following evidence: Vinyl fluoride is closely related structurally to the known human carcinogen, vinyl chloride. The two chemicals cause the same rare tumour (hepatic haemangiosarcoma) in experimental animals, which is also a tumour caused by vinyl chloride in humans.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 73)

Synonyms

- 1-Fluoroethene
- 1-Fluoroethylene
- Monofluoroethene
- Monofluoroethylene

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